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Case Report Rapport de cas

Primary central nervous system T-cell lymphoma mimicking meningoencephalomyelitis in a cat

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(Traduit par les auteurs)

Can Vet J 2013;54:602–605

Case description

A 13-year-old, spayed female, domestic shorthair cat was presented to Guadiamar Veterinary Hospital with a 72-hour history of right head tilt, incoordination, circling to the right side, lethargy and disorientation. The cat was born and lived indoors, without contact with other cats and had a complete vaccination history against feline herpesvirus, calicivirus, parvovirus and feline leukemia virus (Purevax RCP and Purevax FeLV, Mérial, Barcelona, Spain). The vital signs observed were within normal ranges. The neurological examination revealed a decreased mental status, head tilt, and circling to the right, and postural reaction deficits in the right hind limb. A right facial hypoalgesia and positional strabismus of the right eye were found in the cranial nerve assessment. These findings were consistent with a right-sided central vestibular lesion. The results of a white blood (cell) count, biochemical profile, and urinalysis were within normal limits. Corticosteroid therapy (methylprednisolone Solumoderin; Pfizer, Madrid), 2 mg/kg body weight (BW), IM, q24h was administered for 2 d, inducing a distinct improvement in the clinical signs, but a relapse was observed as soon as the treatment was stopped.

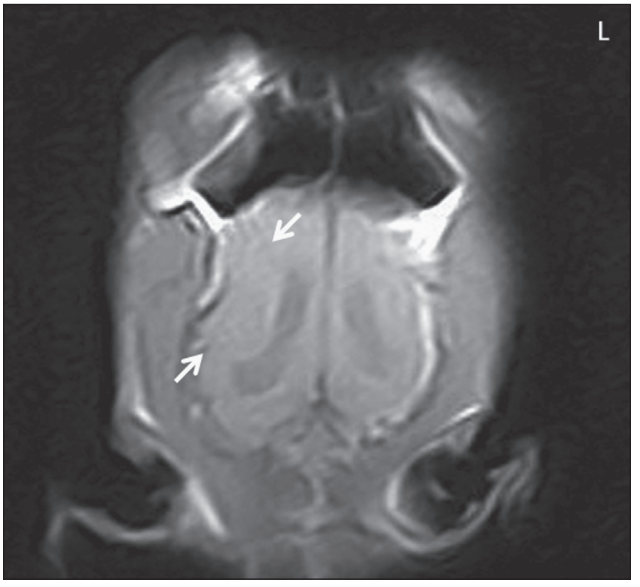

Figure 1. Dorsal T1-weighted MR images at the level of the corpus callosum. Compression of the right lateral ventricle in the temporal cortex without formation of a well-defined mass (arrows). L – left side.

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Table 1. Antibodies and methods used to identify specific cellular and viral markers

Marker	Antibody/clone	Company	Dilution	Method
CD3	Monoclonal/F7.2.38	Dako	1:500	PAP
CD79α	Monoclonal/RB9013P	NeoMarkers	1:250	ABC
CD45R	Monoclonal/B220/Ly5	Linaris	1:1000	ABC
Macrophages	Monoclonal/MAC387	Dako	1:750	LSAB
Borna virus	Monoclonal/p38	L. Stitz,Tübingen	1:1000	LSAB
Feline leukemia virus	Monoclonal/gp70(C11D8)/p27 (PF12J10A)	CMI	1:200/1:100	IPO
Feline infectious peritonitis virus	Monoclonal/FCV3-70	CMI	1:10	PAP
Rabies virus	Polyclonal	Dr. U. Eskens, Giessen	1:500	ABC
Pseudorabies virus	Polyclonal	Dr. U. Eskens, Giessen	1:20000	PAP
Feline herpes virus	Monoclonal/FHV7-7	CMI	1:200	PAP

PAP — Peroxidase antiperoxidase method; ABC — Avidin-biotin peroxidase method; LSAB — Labelled streptavidin-biotin peroxidase method: IPO — Indirect peroxidase method; CMI — Custom monoclonals international.

Dorsal and lateral radiographs of the cranium, thorax, and abdomen were obtained but no abnormalities were detected. The cat was anesthetized for a magnetic resonance imaging (MRI) study of the neurocranium. The anesthetic protocol included medetomidine (Domtor; Esteve, Madrid, Spain), 10 μg/kg BW, IM, methadone (Metasedin; Esteve), 0.3 mg/kg BW, IM, and midazolam (Dormicum; Roche, Madrid, Spain), 0.2 mg/kg BW, IV. Propofol (Vetofol; Esteve), 1 mg/kg BW, IV was used for induction and isoflurane for maintenance (1.5% FI). The obtained sequences were the sagittal, dorsal, and transverse SET1 localizer, which did not show any lesions but a light ventricular asymmetry with narrowed and displaced right lateral ventricle (Figure 1). The cat died suddenly because of cardiorespiratory arrest during the MRI study and no conclusions could be drawn. Encephalomyelitis was suspected based on clinical findings, although other diseases could not be ruled out.

Necropsy revealed gross lesions which were restricted to the brain; there were no changes in other organs. The leptomeninges appeared focally congested and the lateral ventricles and spinal cord canal were moderately dilated. The brain, cerebellum, and spinal cord were fixed in 10% buffered formalin for 10 d and then transversely and sequentially sectioned. Samples of heart, lung, spleen, liver, small and large intestine, kidney, and mediastinal and mesenteric lymph nodes were also collected and fixed in 10% buffered formalin. After routine processing, 4-μm tissue sections were stained with hematoxylin and eosin (H&E), and samples of brain, cerebellum, and spinal cord were also stained with periodic acid-schiff (PAS), Ziehl-Neelsen (ZN), and Giemsa to rule out fungi, bacteria, or viral inclusion bodies, respectively. Demyelination was examined by Luxol fast blue (LFB) and Masson's trichrome staining was performed to detect deposits of connective tissue. Table 1 shows the various antibodies that were used in an immunohistochemical study. In addition, formalin-fixed paraffin-embedded sections of the brain were processed and analyzed by real-time polymerase chain reaction (PCR) for amplification of feline leukemia virus and feline immunodeficiency virus specific genes.

Histologically, thick perivascular cuffs of 8 to 10 rows of small round cells accompanied by a diffuse infiltration into the parenchyma were the main findings (Figure 2). The lesion extended from the frontal lobe of the brain to the brainstem and spinal cord and predominated in the white matter. The infiltrate was relatively uniform and consisted mostly of cells with lymphoid morphology. Some of the cells showed pleomorphism and had large nuclei with coarsely clumped chromatin and scant cytoplasm. Mitoses were occasionally seen. Scarce connective tissue formation arranged concentrically around vessels and between cells was demonstrated with Masson's trichrome stain. Foci of subpial infiltration were also observed in the leptomeninges of the cerebrum, cerebellum, and spinal cord. The parenchyma of the cerebellum was not affected. Additionally, a moderate gliosis as well as neuronophagy and areas of demyelination (evidenced by LFB) were seen. No histopathological lesions were observed in other organs.

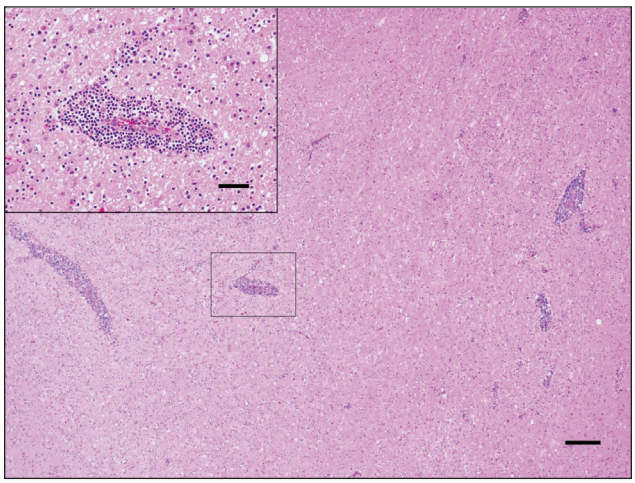

Figure 2. Cervical spinal cord. Thick perivascular cuffs together with a diffuse infiltrate of lymphoid cells and gliosis are seen in the white matter. Hematoxylin and eosin (H&E). Bar = 200 μm. (Inset) – Higher magnification of a thick perivascular cuff. H&E. Bar = 50 μm.

The prominent mononuclear perivascular cuffing and leptomeningeal infiltration of the brain and spinal cord, coupled with diffuse infiltration into the parenchyma yielded a most probable diagnosis of diffuse nonsuppurative meningoencephalomyelitis. Accordingly, the differential diagnosis was widened to include lymphoproliferative diseases. To identify etiological agents, we tested for Borna, feline leukemia virus-antigen, feline infectious peritonitis (FIP) virus-antigen, rabies and pseudorabies virus-antigen, and feline herpes virus-antigen by immunohistochemistry. In addition, we tested for feline leukemia and feline immunodeficiency viruses by real-time PCR. All these tests yielded negative results.

To identify the immunophenotype of the cellular infiltrate, tissue sections were immunostained using antibodies against

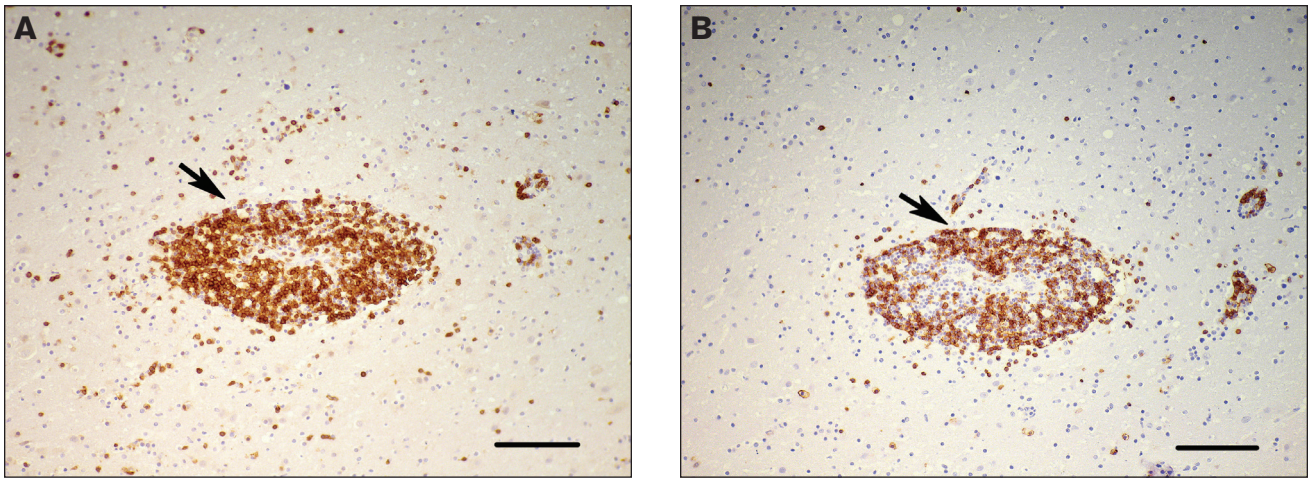

Figure 3. Brain. Serial sections of a perivascular cuff area. Note that the same cells are stained in both (A) and (B) (arrows). A – Lymphoid cells displaying a strong membranous and cytoplasmatic staining with CD3 antibody. Peroxidase antiperoxidase immunohistochemical method. Bar = 100 µm. B – Lymphoid cells displaying a strong membranous and cytoplasmatic staining with CD45R antibody. Avidin-biotin peroxidase immunohistochemical method. Bar = 100 µm.

CD3 (T-cell marker), CD79α (B-cell marker), CD45R (B-cell marker), and MAC387 (macrophage/monocyte marker) antigens. The results showed that most of the infiltrative cells (> 95%) present in brain, spinal cord parenchyma, perivascular spaces, and leptomeninges expressed CD3 (Figure 3A). In addition, the majority of the infiltrative cells (~80%) expressed CD45R also (Figure 3B) while no staining was observed with CD79α antibody. Co-expression of CD3 and CD45R in infiltrative cells was commonly observed (Figures 3A, B). Finally, scattered cells expressed MAC387.

Discussion

In this case report, immunohistochemical results refuted the initial diagnosis of diffuse nonsuppurative meningoencephalomyelitis of unknown etiology in the cat, and pointed to the final diagnosis of diffuse primary central nervous system (CNS) lymphoma.

Primary CNS lymphoma is a rare neoplasm arising within and confined to the CNS; its prevalence is less than 3% of all primary CNS tumors. In veterinary medicine, it has been reported mainly in dogs and rarely in cats, ruminants, and horses (1–3). The median duration of neurologic signs for cats is 30 d (4). In this case the duration of the neurologic signs was only 72 h. Primary CNS lymphoma often presents as a solitary, well-defined, and isolated intraparenchymal mass or as a focally extensive infiltrate in the brain and/or spinal cord which can be detected by MRI or at necropsy (5–10).

In the present case the cat showed a diffuse pattern of lesions accompanied by prominent perivascular cuffs extending from the frontal lobe to the brainstem and spinal cord, which were not detected by MRI or necropsy. In addition, invasion of the meninges was observed. This uncommon pattern of lymphoma, together with the variable and ambiguous clinical presentation, may mimic other neurological processes such as encephalomyelitis, making it difficult to make an accurate early diagnosis. There are few reports in cats in which a cranial radiographic study was performed but no abnormalities were evident, as in our case (6,10). There have, however, been a few reports on the MRI findings of primary CNS lymphomas in cats not showing the characteristic MRI features (4–7).

The fungal and bacterial etiologies were excluded in our case by the negative results of PAS, Giemsa, and Ziehl Neelsen staining. The lack of protozoan oocysts (confirmed by histopathology and negative Giemsa stain) ruled out infection with protozoa.

The fact that the cat lived indoors and had a complete vaccination history made viral infections unlikely. Moreover, the lack of detection of viral antigens by immunohistochemical and PCR methods ruled out infection by FIP, feline leukemia, feline immunodeficiency, Borna, rabies, pseudorabies, and feline herpes viruses. Infection by Borna virus is characterized by a nonsuppurative meningoencephalomyelitis, predominantly in the gray matter, with prominent perivascular cuffs of histiocytes and lymphocytes in the cortex, brainstem, and spinal cord but with predominance in the hippocampus (11,12). However, the negative immunohistochemical labelling did not support a diagnosis of Borna disease.

Autoimmune disorders such as granulomatous meningoencephalomyelitis (GME) and necrotizing meningoencephalitis (NME) were discarded based on histopathology and MAC387 immunolabelling. The inflammatory infiltrate in GME is distributed in almost all parts of the CNS and contains more histiocytes, which in the chronic stage transform to epithelioid cells that can form discrete cohesive sheets or granuloma-like lesions. In NME the reaction is mostly in the cortical gray matter and is characterized by lymphocytes, plasma cells, and monocytes with evidence of cerebral necrosis (13).

Most primary CNS lymphomas in animals are of T-cell type, unlike in humans (14). The T-immunophenotype was based on the expression of CD3 by the majority of cells and their lack of staining with CD79α antibody. However, the majority of infiltrative cells co-expressed CD45R. Although CD45R antibody has been considered to be specific for the identification of B-cells (15), there is evidence suggesting that the epitope recognized by this antibody may also be expressed

in activated T-cells, predominantly CD8 T-cells (16). Human CD79α antibody, however, is one of the most specific markers for B-lineage derivation (17) and has been shown to cross-react with feline tissues (9,10,18).

T-cell lymphoma and non-suppurative meningoencephalomyelitis are both characterized by marked infiltrates of small lymphocytes that cannot be distinguished by histology. Immunophenotyping is an important diagnostic tool in differentiation between inflammation and lymphomas when histological changes are ambiguous.

In summary, the present study indicates that primary CNS T-cell lymphoma may be present with variable clinical, imaging, and histological features that might complicate the differentiation between inflammatory and neoplastic lesions. Accordingly, this disorder should be included in the differential diagnosis of diffuse brain lesions and the use of neuroimaging and immunohistochemical techniques is advised in order to obtain an accurate diagnosis.

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